

Full Text HL-97-005

TISSUE ENGINEERING, BIOMIMETICS, AND MEDICAL IMPLANT SCIENCE

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National Heart, Lung, and Blood Institute

National Institute of Dental Research

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: July 1, 1997

Application Receipt Date: August 25, 1997

THIS RFA USES "MODULAR GRANT" AND "JUST-IN-TIME" PROCEDURES. THIS COMPLETE RFA INCLUDES THE MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS WHICH MUST BE USED WHEN PREPARING APPLICATIONS TO THIS RFA.

PURPOSE

The National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Dental Research (NIDR), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invite applications to design and engineer natural and novel approaches for the repair, restoration, and replacement of tissues and whole organs based on a comprehensive scientific understanding of biological structures and their function. The overall goal of this RFA is to facilitate multidisciplinary research, design, and training aimed at development of a new generation of natural and synthetic medical implants, including totally biological solutions for instances in which synthetic implants have historically been used.

Research projects focusing on devices intended primarily for short term use, specifically 24 hours or less (e. g., hemodialysis and cardiopulmonary bypass), will not be considered to be responsive to this RFA.

This Program will support both design directed and hypothesis driven research applicable to the missions of NHLBI, NIDR, and NIAMS. Applicants are encouraged to indicate to which institute, NHLBI, NIDR, or NIAMS, their application should be directed.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000", a PHS led national activity for setting priority areas. This Request For Applications, "Tissue Engineering, Biomimetics, and Medical Implant Science", is related to the priority areas of heart disease and stroke, oral health, immunization and infectious diseases, cancer, diabetes, and musculoskeletal injuries and diseases. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock 017-001-00474-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic non-profit and for-profit organizations, public and private, such as universities, colleges, companies, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal Government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators. Applications from foreign institutions will not be accepted. However, subcontracts to foreign institutions are allowable, with sufficient justification.

MECHANISMS OF SUPPORT

Support of this program will be through NHLBI, NIDR, and NIAMS. The mechanisms available for support of applications to this RFA include individual research project grants (R01) and collaborative R01 projects. In the case of collaborative R01 projects, a group of investigators may submit simultaneously at least 3, and no more than 5, R01s with a common theme. Collaborative R01 projects may be from a single institution or several institutions, may include

shared resources, and must demonstrate the interdependence of the individual components. All RO1 applications, both collaborative and individual, must provide evidence that the research will be multidisciplinary in nature; applicants are encouraged to specify how the research will further the objectives of both NHLBI, NIDR, and NIAMS.

Specific RO1 application instructions are modified to include "MODULAR GRANT" AND "JUST-IN-TIME" streamlining efforts being examined by the NIH. The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budget information is required under this approach. The just-in-time procedure allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, applicant institutions, reviewers, and NIH staff.

For this RFA, funds must be requested in \$25,000 direct cost modules, up to a maximum of eight modules (\$200,000 direct costs) per year, per RO1, whether individual or collaborative. A feature of the modular grant is that no escalation is provided for future years, and all anticipated expenses for all years of the project must be included within the number of modules being requested. Only limited budgetary information will be required and any budget adjustments made by the Initial Review Group will be in modules of \$25,000. Instructions for completing the Biographical Sketch have also been modified. In addition, Other Support information and the application Checklist page are not required as part of the initial application.

If there is a possibility for an award, necessary budget, Other Support and Checklist information will be requested by NHLBI, NIDR, or NIAMS staff following the initial review. The APPLICATION PROCEDURES section of this RFA provides specific details of modifications to standard PHS application kit procedures.

Upon initiation of the program, NHLBI will sponsor annual meetings, most likely to be held in Bethesda, Maryland, to encourage exchange of information among investigators who participate in this program. In considering the number of modules to request, budget projections should include travel funds that will allow principal investigators, other key research scientists, and young investigators to participate in these meetings.

Applicants are expected to furnish their own estimates of time required to achieve the objectives of the proposed research project. Since a variety of approaches would represent valid responses to this RFA, it is anticipated that there will be a range of costs among individual grants awarded.

There may be another open competition at the end of this program. If not, future unsolicited competing applications will compete with all investigator-initiated applications and be reviewed

according to the customary peer review procedures. It is anticipated that support for this program will begin in April 1998. Administrative adjustments in project period and/or amount may be required at the time of the award.

FUNDS AVAILABLE

NHLBI and NIDR will each allocate approximately \$2 million in direct costs (approximately \$3 million in total costs) to support projects from this RFA during FY 98. It is anticipated that about 4 or 5 collaborative R01 projects consisting of 3 to 5 individual R01s per project will be awarded, and that in addition 6 to 8 individual R01s will be awarded, provided that the applications are of high scientific merit. Although NIAMS has an interest in collaborative projects, for this RFA only, NIAMS will allocate approximately \$400,000 in direct costs (approximately \$600,000 in total costs) for FY 98 to support 2 to 3 individual R01's, provided that the applications are of high scientific merit. It is possible that a collaborative project in a topic area that overlapped the interests of NIAMS and NIDR could be co-funded by these two institutes if the project was of high scientific merit. The maximum total costs for the first year of a collaborative R01 project are \$1 million. Direct costs will be awarded in modules of \$25,000, less any overlap or other necessary administrative adjustments. Facilities and administrative (indirect) costs will be awarded based on the negotiated rates. Applicants may request up to five years of support. Although this program is provided for in the financial plans of NHLBI, NIDR, and NIAMS, the award of grants pursuant to this RFA is contingent upon the receipt of a sufficient number of high quality applications and the availability of funds for this purpose. Policies that govern research grant programs of the National Institutes of Health will prevail.

RESEARCH OBJECTIVES

Background

Biomimetics is an emerging interdisciplinary field that combines information from the study of biological structures and their functions with physics, mathematics, chemistry and engineering in the development of principles that are important for the generation of novel synthetic materials and organs. Tissue engineering is the application of these principles for the restoration, repair, replacement and assembly of functional tissues and organs. Medical implant science is the application of scientific and clinical principles to the design, fabrication, and evaluation of medical implants. In the area of heart, lung, and blood diseases, principles from tissue engineering, biomimetics, and medical implant science have been applied to the development and design of mechanical and bioprosthetic heart valves, prosthetic vascular grafts, vascular stents, infusion

pumps, pacemakers, and implantable cardiac defibrillators. In the area of oral, craniofacial, and dental disease, principles from tissue engineering, biomimetics, and medical implant science are applied to developing dental and facial implants, temporomandibular joint (TMJ) prostheses, formation of bone matrix substitutes, and artificial replicas of bone, skin, and mucosa. In the area of musculoskeletal injury and disease, principles from tissue engineering, biomimetics, and medical implant science are applied to developing orthopaedic implants/prostheses, and assessing the biologic response to formation of bone and connective matrix substitutes and artificial replicas of bone, connective tissues, and skin.

Advances in engineering materials for such uses include new biodegradable polymers for controlled, site-directed delivery of drugs, gene vectors, antisense oligonucleotides, and growth factors that stimulate angiogenesis, revascularization, and repair, or inhibit thrombosis, cellular hyperplasia, and infection; synthetic biodegradable polymeric scaffolds for construction of heart valve leaflets from autologous cells; construction of vascular grafts from autologous cells grown on synthetic templates or scaffolds; new polymers for guided tissue regeneration used in treating periodontal disease and bone and connective tissue defects; demineralized allogenic bone matrix for craniofacial and other bone reconstruction procedures; coral-based hydroxyapatite replicas for reconstruction of alveolar ridges and other osseous defects; dermal/epidermal skin substitutes; fibrin-based sealants to weld tissues and blood vessels in a variety of surgical settings; and synthetic, biodegradable polymeric scaffolds for bone, cartilage, ligament, tendon, and meniscal repair from autologous cells. Most implants have resulted in improving the quality of life and saving or prolonging lives. However some implants, such as TMJ prostheses and certain heart valve designs, have failed catastrophically. For orthopaedic implants, osteolysis has emerged as a major problem.

Rationale

There is a need for a firmer scientific and technical basis in order to develop the next generation of medical implants that are safe, reliable, "smart", and long-lasting. Integrated and multidisciplinary research should advance our understanding of biological systems and provide the bases for the design and development of novel synthetic medical materials that are compatible with the environment of the host and significantly increase the functional lifetime of implants. Future advances in this field will require materials and computer scientists, physicists, bioengineers, clinicians, biologists, and industry working together towards a shared vision rather than pursuing their separate objectives as has commonly been the case.

Additional factors that have inhibited progress in tissue engineering, biomimetics, and medical implant science are the current concerns of medical device manufacturers over medical liability,

regulatory issues, and public payment policy for experimental implants. In response to the scientific opportunities and public concerns in this area, the National Institutes of Health (NIH) convened two workshops, October 16-17, 1995 and September 24-26, 1996, bringing together more than 150 university, industry, and government specialists in biomaterial, biomimetics, tissue engineering, medical implant, biological and clinical sciences. These experts were charged with recommending research directions that would advance this important field. They agreed that progress in characterization and rational synthesis of advanced biomaterials, together with advances in understanding the molecular basis of biological responses, has set the stage for an integrated approach and ultrastructural basis for advancing biomaterials, tissue engineering, biomimetics, and medical implant science. The specific research and career recommendations of these two groups and which guide this RFA were:

- o Designing and developing biomaterials and implants endowed with desirable biological structures and functions for the treatment of various disorders. This will involve multidisciplinary approaches to synthesizing new, perhaps "smart" or self-monitoring, biomaterials designed for cell, drug, and gene based therapies.
- o Advancing the scientific basis for predicting quality and lifetime of implants, and improving the efficiency of assessing human acceptance of implants. Potential approaches include a focus on reliability, accelerated testing, failure analysis, imaging models, biosensors, and improved understanding of the tissue implant interface.
- o Fostering biomimetics, new tissue engineering processing and advanced manufacturing technologies.
- o Enhancing research careers with new cross-disciplinary strategies in tissue engineering, biomimetics and medical implant science.

One intent of this RFA is to encourage and promote multidisciplinary research on tissue engineering, biomimetics, and medical implant science. Applicants for both individual and collaborative R01s are, therefore, encouraged to include on research teams individuals whose expertise broadens the scope of the scientific approach of the team. The type of expertise and justification for addition of the individual, proposed percent effort, biographical sketch, and letters of agreement to join the team from the applicant and his/her supervisor in the event that the application is funded, must be provided in the application.

An additional intent of the RFA is to encourage new investigators to enter this area of research. These may be senior investigators who have no previous experience in this field, or scientists from any field who are at the beginning stages of their research careers.

Applicants are encouraged to include either category of new investigator on their research team.

In addition, applications are encouraged from new investigators of either category.

PROPOSED RESEARCH

The following research topics are provided as examples, and are not intended to be inclusive or restrictive:

- o explore novel scientific bases for designing and developing medical implants (e.g., autogeneration of a coronary artery, a tooth organ, or articular cartilage);
- o development of advanced methodologies for evaluating the cellular responses to implants, such as fibrous encapsulation, osteolysis, and infection; identification of inflammatory mediators; use of in vitro and in vivo models to predict short- and long-term human responses; understanding the biology of biointegration, biofilm formation, and osteolysis;
- o development of computer/mathematical modeling systems for evaluation of TMJ and other joint biomechanics; creation of a new generation of biomaterials which will permit effective repair or replacement of bone, cartilage, and other connective tissue structures in the TMJ and other joints and their associated muscles;
- o development of heart valves, small-diameter blood vessels, and other organs and tissues for use in the systemic, pulmonary, and craniofacial circulations, using autologous cells in bioreactors, and synthetic biodegradable matrices, scaffolds, mandrels, or other innovative means;
- o design of matrices that would promote the formation of facial musculature, neurological pathways, bone, connective tissues, and skin for use in the repair of orofacial, cardiovascular, pulmonary, and musculoskeletal disorders;
- o use of high resolution cellular and molecular imaging techniques to evaluate the interface between implants and their biological environment, including methods for imaging dynamic and living structures;

o use of computational fluid mechanics for improved design of implants for the management of cardiovascular, pulmonary, hematologic, and musculoskeletal disorders;

o advancement of the fundamental knowledge of biomineralization, including biomineralization precursor phases, microstructure formation, templating, growth, and morphogenesis of bones and teeth;

o development, for drug and cell delivery in applications to tissue engineering, biomimetics, and medical implant science, of "smart" biomaterials that can act as molecular switches to control biological functions and sense environmental changes (e.g., delivery of iron chelators for the treatment of conditions characterized by iron overload); delivery of growth factors, cytokines, chemotactic agents, morphogenic proteins, and other biological factors influencing the repair and regeneration of myocardium, the orofacial complex, skin and musculoskeletal tissues;

o development of cell-specific systems for gene delivery applicable to oral, craniofacial, and skin and musculoskeletal disorders (e.g., salivary gland disorders, orofacial neoplasias, or osteogenesis imperfecta);

o use of combinatorial chemistry for rapid development of lead compounds for basic research and drug discovery applied to tissue engineering, biomimetics, and medical implant science, and development of time and site specific systems for their delivery;

o identification of stem cells and immature committed cells for tissue repair other than for burns or other traumatic injury; development of culture systems (e.g., biodegradable scaffolds, templates, or extracellular matrix analogues) that allow cells to adopt their three-dimensional architecture and to be suitable for transplantation or repair; and

o investigations of the molecular basis of tissue maintenance and regeneration as applied to tissue engineering, biomimetics, and medical implant science (e.g. cell-cell interactions, extracellular matrix, or apoptosis), in instances other than following burns or other traumatic injury.

All submissions must be pertinent to the objectives of the RFA.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN
SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies concerning the inclusion of minorities in study populations which have been in effect since 1990. The new policy contains some new provisions that are substantially different from the 1990 policies. All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513), and reprinted in the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994. Investigators may obtain copies from these sources or from the program staff listed under INQUIRIES.

LETTER OF INTENT

Prospective applicants are asked to submit, by July 1, 1997, a letter of intent. This should include the number and title of this RFA (HL-97-005; "Tissue Engineering, Biomimetics, and Medical Implant Science"), a descriptive title of the proposed research, the names, addresses, and telephone numbers of the Principal Investigator(s), and the identities of other key personnel and participating institutions. The letter of intent is to be addressed to Dr.C. James Scheirer at the address listed under APPLICATION PROCEDURES.

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains is helpful in planning for the timely review of the applications. It allows NHLBI, NIDR, and NIAMS staff to estimate the potential review workload and to avoid possible conflicts of interest in the review.

APPLICATION PROCEDURES

Prospective applicants are encouraged to communicate with program and grants management staff of NHLBI's, NIDR's and NIAMS's Divisions of Extramural Research as early as possible in the planning phase of application preparation. Advice and suggestions by staff may materially assist applicants to ensure that the objectives and structure and the budget format are acceptable.

Applications must be prepared on form PHS 398 (Rev. 5/95). An Application for a PHS Grant is available at most institutional business or grants and contracts offices and may be obtained from the Office of Grants Information, Division of Research Grants (DRG), National Institutes of Health, Suite 3032, 6701 Rockledge Drive, Bethesda, MD 20892 (Telephone: 301/ 435-1099). The instructions accompanying Form PHS 398 must be followed as far as possible.

THE RFA LABEL FOUND IN THE PHS 398 APPLICATION FORM MUST BE AFFIXED TO THE BOTTOM OF THE FACE PAGE OF THE APPLICATION. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. IN ADDITION, THE RFA TITLE AND NUMBER, "Tissue Engineering, Biomimetics, and Medical Implant Science" HL-97-005," MUST BE TYPED ON LINE 2 OF THE FACE PAGE OF THE APPLICATION FORM AND THE YES BOX MUST BE MARKED.

APPLICANTS WITHOUT PRIOR R29 OR R01 SUPPORT, AND NEW INVESTIGATORS TO THE FIELD, ARE STRONGLY ENCOURAGED TO IDENTIFY THEIR STATUS AS A NEW INVESTIGATOR IN A COVER LETTER AND IN THE APPLICATION.

This RFA is restricted to R01 grants. All applications must be submitted as modular grants. The modular grant concept establishes specific modules (increments) in which direct costs may be requested, and the maximum level for requested direct cost. Only limited budgetary information is required in the application; a detailed budget need not be provided.

Sample budgets and justification page will be provided upon request or following the submission of a letter of intent.

In the case of collaborative R01 projects, the individual R01s comprising the project must be submitted as one packet accompanied by a cover letter which lists the principal investigators of each R01, their institution, and their project title, and defining how and why the individual participants propose to collaborate.

BUDGET INSTRUCTIONS

The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

- o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD Do not complete Form

Page 4 of the PHS 398 (rev 5/95). It is not required nor will it be accepted at the time of application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT Do not complete the categorical budget tables on Form page 5 of the PHS 398 (rev. 5/95). Only the requested total direct costs line for each year must be completed based on the number of \$25,000 modules being requested. Applicants may not request a change in the amount of each module. A maximum of EIGHT modules (\$200,000 direct costs) per year may be requested and each applicant may request up to FIVE years of support for this RFA. Direct cost budgets will remain constant throughout the life of the project (i.e., the same number of modules requested for all budget periods). Any necessary escalation should be considered when determining the number of modules to be requested. However, in the event that the number of modules requested must change in any future year due to the nature of the research proposed, appropriate justification must be provided. Total Direct Costs for the Entire Proposed Project Period should be shown in the box provided.

o BUDGET JUSTIFICATION

Budget justifications should be provided under "Justifications" on Form Page 5 of the PHS 398.

List the names, role on the project and proposed percent effort for all project personnel (salaried or unsalaried) and provide a narrative justification for each person based on his/her role on the project. Identify all consultants by name and organizational affiliation and describe the services to be performed.

Provide a general narrative justification for individual categories (equipment, supplies, etc.) required to complete the work proposed. More detailed justifications should be provided for high cost items. Any large one-time purchases, such as equipment requests in excess of \$10,000, must be accommodated within these limits.

The budget should include a request for funds for attendance at an annual meeting of the principal investigators and other key investigators including young investigators and investigators new to the field.

o CONSORTIUM/CONTRACTUAL COSTS - If collaborations or subcontracts are involved that require transfer of funds from the grantee to other institutions, it is necessary to establish formal subcontract agreements with each collaborating institution. A letter of intent from each

collaborating institution should be submitted with the application. Only the percentage of the consortium/contractual TOTAL COSTS (direct and indirect) relative to the total DIRECT COSTS of the overall project needs to be stated at this time. The following example should be used to indicate the percentage cost of the consortium, "The consortium agreement represents 27% of overall \$175,000 direct costs requested in the first year.". A budget justification for the consortium should be provided as described in the "Budget Justification" section above (no Form Page 5 is required for the consortium). Please indicate whether the consortium will be in place for the entire project period and identify any future year changes in the percentage relative to the parent grant.

If there is a possibility for an award, the applicant will be requested to identify actual direct and indirect costs for all years of the consortium. Please note that total subcontract costs need not be calculated in \$25,000 modules. However, when subcontract funds are added to the parent grant budget, the total direct cost amount must be included in the number of \$25,000 modules requested.

o BIOGRAPHICAL SKETCH - A biographical sketch is required for all key personnel, following the modified instructions below. Do not exceed the two-page limit for each person.

Complete the educational block at the top of the form page; List current position(s) and those previous positions directly relevant to the application; List selected peer-reviewed publications directly relevant to the proposed project, with full citation; The applicant has the option to provide information on research projects completed and/or research grants participated in during the last five years that are relevant to the proposed project.

o OTHER SUPPORT - Do not complete the "Other Support" pages (Form Page 7). Selected other support information relevant to the proposed research may be included in the Biographical Sketch as indicated above. Complete Other Support information will be requested by NHLBI staff if there is a possibility for an award.

o CHECKLIST - No "Checklist" page is required as part of the initial application. A completed Checklist will be requested by staff if there is a possibility for an award.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

Applicants from institutions which have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. In such a case, a letter of agreement from either the GCRC program director or principal investigator should be included with the application.

APPLICATIONS NOT CONFORMING TO THESE GUIDELINES WILL BE CONSIDERED UNRESPONSIVE TO THIS RFA AND WILL BE RETURNED WITHOUT FURTHER REVIEW.

Submit a signed, typewritten original of the application, including a cover letter (if appropriate) and three signed photocopies, in one package to:

Division of Research Grants (DRG)
National Institutes of Health
6701 Rockledge Drive, Room 1040-MSC 7710
Bethesda, MD 20892 (use 20817 for Federal Express)

At the time of submission, three additional copies of the application must also be sent to:

Dr. C. James Scheirer
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
Rockledge Building 2, Room 7220
6701 Rockledge Drive
Bethesda, MD 20892

Applications must be received by August 25, 1997. If an application is received after that date, it will be returned to the applicant without review.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by DRG and responsiveness by NHLBI, NIDR, and NIAMS. Incomplete applications will be returned to the applicant without further consideration. If NHLBI, NIDR, and NIAMS staff find that the application is not responsive to the RFA, it will be returned without further consideration. Remaining applications may be subjected to a streamlined review process by a Special Emphasis Panel convened by NHLBI, NIDR, and NIAMS Scientific Review Offices, to determine their scientific merit relative to other applications received in response to the RFA. The roster of reviewers for the RFA will be

available on the NHLBI home page approximately four weeks prior to the scheduled review date. Applications determined to be meritorious will be evaluated for scientific and technical merit by the review committee, be discussed and receive a priority score. All other applications will not be discussed or scored. The initial review group will evaluate all R01s, whether single or collaborative, as individual investigator-initiated grant applications. Additionally the IRG will comment on the overall strength and likelihood of effective collaboration of each collaborative program, and on the multidisciplinary nature of both individual and collaborative R01s. Each R01 within a collaborative program will receive a priority score. Secondary review of the applications will be conducted by the National Heart, Lung and Blood Advisory Council (NHLBAC), the National Advisory Dental Research Council (NADRC), and the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council (NAMSAC).

Major factors to be considered in the evaluation of the applications include:

- o the degree of innovativeness of the approaches proposed;
- o the likelihood of success of the research objectives proposed;
- o the scientific merit of all components of the proposed research project, including its significance, originality, feasibility, and experimental design;
- o the degree to which the project will represent collaborative research among investigators from different disciplines within an individual R01, or among individual R01s submitted as a collaborative R01 project, and the likelihood of effective collaboration among the investigators;
- o the qualifications and research experiences of the collaborating investigators;
- o the likelihood that the proposed research will advance the fund of knowledge in tissue engineering, biomimetics, and medical implant science for application to heart, lung, and blood diseases, oral health, musculoskeletal and skin diseases, as well as other fields; and
- o the ability to recruit individuals from appropriate study populations (i.e., women, subpopulations of minorities and disabled individuals) as defined by the NIH guidelines along with provisions for their protection from research risks and the humane treatment of animal research subjects that may be used.

The personnel category will be reviewed for appropriate staffing based on the requested percent effort and justification provided. The direct costs budget request will be reviewed for consistency with the proposed methods and specific aims. Any budgetary adjustments recommended by the reviewers will be in \$25,000 modules. The duration of support will be reviewed to determine if it is appropriate to ensure successful completion of the requested scope of the project.

AWARD CRITERIA

Applications will receive a secondary level of review by NHLBI's, NIDR's, and NIAMS's Advisory Councils in May 1998. The earliest anticipated date of award is July 1998. Applicants should be aware that, in addition to scientific merit, program priorities and program balance, the total cost of the proposed project and the availability of funds will be considered by NHLBI, NIDR, and NIAMS staff as well as the NHLBAC, NADRC, and NAMSAC in making funding recommendations.

In addition, NHLBI, NIDR, and NIAMS appreciate the value of complementary funding from other public and private sources including foundations and industrial concerns. In circumstances in which applications have similar scientific merit, but vary in cost competitiveness, NHLBI, NIDR, and NIAMS are likely to select the more cost competitive application for funding.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Dr. Paul Didisheim
Head, Biomaterials Program
Division of Heart and Vascular Diseases
National Heart, Lung and Blood Institute
Rockledge 2 Building, Room 9180
Bethesda, MD 20892-7940
Telephone: 301-435-0513
FAX 301-480-1336
E-mail: pd16i@nih.gov

Dr. Eleni Kousvelari
Program Director for Biomaterials, Biomimetics, and Tissue

Engineering

Division of Extramural Research

National Institute of Dental Research

Natcher Building, Room 4AN 18A

Bethesda, MD 20892-6402

Telephone: 301-594-2427

FAX: 301-480-8318

E-mail: kousvelari@de45.nidr.nih.gov

Dr. James S. Panagis

Director, Orthopaedics Program

National Institute of Arthritis and Musculoskeletal and Skin
Diseases

Natcher Building, Room 5AS 37K

Bethesda, MD 20892-6500

Telephone: 301-594-5055

FAX: 301-480-4543

E-mail: panagisj@ep.niams.nih.gov

Direct inquiries regarding grants management issues to:

Mr. William Darby

Division of Extramural Affairs

National Heart, Lung, and Blood Institute

Rockledge Building 2, Room 7128

6701 Rockledge Drive

Bethesda, MD 20892-7924

Telephone: 301-435-0177

FAX: 301-480-3310

Email: darbyw@gwgate.nhlbi.nih.gov

Mr. Martin R. Rubinstein

Division of Extramural Research

National Institute of Dental Research

Natcher Building, Room 4AN 44A

Bethesda, MD 20892-6402

Telephone: 301-594-4800

FAX:

E-mail: Martin.Rubinstein@nih.gov

Ms. Vicki Maurer

Grants Management Specialist

National Institute of Arthritis and Musculoskeletal and Skin
Diseases

Natcher Building, Room 5AS 49A

Bethesda, MD 20892-6500

Telephone: 301-594-3504

FAX: 301-480-5450

E-mail: maurerv@ep.niams.nih.gov

The National Institute of General Medical Sciences (NIGMS) has an interest related to this RFA.
Direct inquiries regarding this interest to:

Dr. Scott Somers

National Institute of General Medical Sciences

Natcher Building, Room 2AS 49J

Bethesda, MD 20892-6402

Telephone: 301-594-5560

FAX: 301-480-2802

E-mail: somerss@gm1.nigms.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.121, 93.837, 93.838, 93.839, and 93.846. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The Public Health Service strongly encourages all grant recipients to provide a smoke free workplace and promote the non use of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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